

Quality by Design-Based RP-HPLC Method Development and Validation for Analysis of Rivaroxaban in Bulk and Tablet Formulations

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Abstract

Introduction: A Quality by Design (QbD)-driven RP-HPLC method was systematically developed and validated for the accurate quantification of Rivaroxaban in bulk and tablet formulations. Unlike conventional trial-and-error methods reported in the literature, the QbD approach offers a more scientific, risk-based, and structured framework that enhances method understanding and robustness. **Material and Methods:** Key Critical Process Parameters (CPPs)—such as flow rate, mobile phase composition, and detection wavelength—were optimized using Design Expert 11 software. Their effects on Critical Quality Attributes (CQAs) including retention time, peak area, and theoretical plates were evaluated through a 3^3 factorial design. Rivaroxaban, a direct oral anticoagulant approved for the prevention of venous thromboembolism following hip or knee replacement surgery, was analyzed using a Cosmosil C18 column (4.6 × 250 mm), with a flow rate of 1.0 mL/min and UV detection at 249 nm. **Results:** The method showed excellent linearity (5–30 ppm) and was validated as per ICH Q2 (R1) guidelines, demonstrating superior accuracy, precision, and robustness. **Conclusion:** The QbD-based method provides better control over variability and ensures consistent performance, making it highly suitable for routine quality control of Rivaroxaban formulations.

Keywords: HPLC, Rivaroxaban, Validation, QbD, Linearity

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Introduction

Quality by Design (QbD) is a systematic approach to method development. It starts with clearly defined objectives and focuses on understanding the product and process, along with implementing effective process control. This framework is built upon solid scientific principles and robust quality risk management.^[12] The QbD methodology enhances product quality assurance, offers regulatory flexibility, and fosters continuous improvement by emphasizing a deep understanding of both the product and the process, coupled with quality risk management and controls. The foundations of the QbD method are rooted in the guidelines set forth by ICH Q8 (Pharmaceutical Development), ICH Q9 (Quality Risk Management), and ICH Q10 (Pharmaceutical Quality System).^[18]

Analytical science is crucial throughout the pharmaceutical product lifecycle, evolving concurrently with product development. Analytical QbD applies a science and risk-based approach to analytical method development. Its goal is to comprehend predefined objectives, thereby controlling critical method variables that influence critical method attributes. This leads to improved method performance, enhanced robustness, greater ruggedness, and flexibility for ongoing refinement. The outcome of QbD is a well-understood, fit-for-purpose, and robust method that

consistently delivers reliable results throughout its lifecycle, mirroring the benefits seen in process QbD.^[20,21]

For QbD-compliant High-Performance Liquid Chromatography (HPLC) methods, assessing robustness and ruggedness early in the development phase is essential to ensure the method's efficiency over the product's lifetime. Neglecting this can lead to significant time and resource expenditure in redeveloping, revalidating, and retransferring analytical methods if an unreliable system is adopted. The primary aim of AQbD is to pinpoint potential failure modes and establish a resilient method operable design region, or design space, within meaningful system suitability criteria, all while managing the method's lifecycle continuously. Numerous studies in the literature have reported the successful application of QbD approaches to HPLC method development.^[22]

Anticoagulants are frequently prescribed to inhibit the development of new blood clots or to curtail the growth of existing ones. Unchecked, these clots can impede blood circulation, leading to severe health events like myocardial infarctions or cerebrovascular accidents. Rivaroxaban (RIX), an oral anticoagulant, has received approval from both the U.S. Food and Drug Administration (FDA) and the European Commission. Its approved use in adults is for the prophylaxis of venous thromboembolism, especially following total hip or knee arthroplasty.^[1,2]

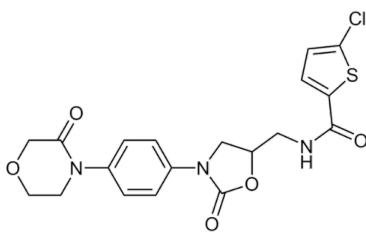


Figure 1: Structure of Rivaroxaban

Although RP-HPLC methods for Rivaroxaban (RIV) analysis exist, the innovation of this study lies in its pioneering adoption of a Quality by Design (QbD) framework. Our systematic development process, which incorporated a 3^3 -factorial design and was refined using Design Expert 11 software, enabled a thorough elucidation of the critical process parameters and critical quality attributes. This QbD- approach yielded an efficient method that employs a notably simple mobile phase, eliminating the need for buffer preparations or ion-pairing reagents, and offering a quick run time. Consequently, this method is highly advantageous for routine quality control of numerous samples, marrying efficiency with robust analytical performance. Quality by Design (QbD) is a systematic approach to pharmaceutical development that focuses on designing and controlling processes to ensure product quality. Instead of testing for quality after the fact, QbD emphasizes understanding the product and process from the outset and integrating quality into the design phase.^[14]

Material And Methods

Rivaroxaban standard is obtained from Megafine Pvt. Ltd. Mumbai along with CoA. HPLC Water and Acetonitrile were of analytical grade and purchased by Variety Traders, Amravati.

Apparatus And Chromatographic Conditions

RP-HPLC analysis was performed on an Agilent 1100 series system. Separation were done on a Cosmosil C₁₈ Column (250 x 4.6mm). In the chromatographic condition of the optimized trial, the flow rate was 1.0 mL min⁻¹ and the column temperature was set at 37.5⁰ C while using isocratic elution with ACN: Water (50:50 v/v) mixture. Injection volume was 10uL and UV Detection was performed at 249nm. Peak identity was confirmed by retention time comparison.

Standard preparation

10mg of Rivaroxaban drug was accurately weighed and transferred into 10ml of volumetric flask and the volume was made with a small amount of mixture of ACN: Water (80:20 v/v), then sonicated it for 2min and made up to the mark with ACN: Water (80:20 v/v) to get the concentration of the 1000 ppm. From this 0.1 ml was pipetted out and transferred into 10ml of volumetric flask and the volume was made up to the mark with ACN: Water (80:20 v/v) to get 10ppm solution and its absorbance was measured at 249 nm.

Test preparation

To determine the content of Rivaroxaban from the marketed formulation, 20 tablets were weighed, triturated, and the average weight was calculated and the amount of tablet powder equivalent to 10mg of Rivaroxaban was weighed accurately and transferred to a 10ml volumetric flask. Sufficient amount of ACN: Water (80:20 v/v) was added and sonicated for 10 minutes and the solution was diluted up to the mark with the same solvent. An aliquot was then removed and centrifuged at 5000 rpm for 10 min, the solution was filtered using 0.45um membrane filtration assembly. From the filtrate, the measured volume was taken and diluted with ACN: Water (80:20 v/v) to get the final concentration. The absorbances were measured at selected wavelengths.

Roadmap For QbD

Defining the Quality Target Product Profile

The Quality Target Product Profile (QTPP) is instrumental in identifying the variables that influence its defined parameters. For the proposed High-Performance Liquid Chromatography (HPLC) method, critical QTPP elements identified include retention time, theoretical plate count, and peak area.

Determining Critical Quality Attributes

Critical Quality Attributes (CQAs) are defined as method parameters that directly impact the QTPP. To maintain the QTPP within an acceptable response range, mobile phase composition, flow rate, and column temperature were identified as critical method parameters requiring stringent control.^{21,22}

Factors and their Levels

Table 1: Independent Variables and their Levels

Independent Variables	Low	Medium	High
A = Mobile Phase Ratio (v/v); X ₁	45:55	50:50	55:45
B = Flow Rate (ml/Min); X ₂	0.8	1.0	1.2
C = Temperature ; X ₃	35	37.5	40

Table 2: Dependent Variables and their Types

Dependent variables	Types
Y1	Retention Time
Y2	Area
Y3	Theoretical Plates

Application of 3³ Factorial Design by Design Expert Software

So by using the Box-Behnken Design to systematically investigate the influence of critical process parameters (CPPs) on the critical quality attributes (CQAs) of the RP-HPLC method, a 3^3 factorial design was employed. This

Table 3: Trials As Per Design Expert For 3³ Factorial Design

<i>Trial No</i>	<i>Mobile Phase ratio (v/v) (X₁)</i>	<i>Flow Rate (mL/min) (X₂)</i>	<i>Temp (°C) (X₃)</i>	<i>RT (Min)(Y₁)</i>	<i>Theoretical Plates (Y₂)</i>	<i>Assymetry (Y₃)</i>
1	55:45	1.2	40	3.15	10807	1.46
2	55:45	1	40	3.78	12270	1.21
3	55:45	0.8	40	4.72	14403	1.31
4	55:45	1.2	37.5	3.16	10688	1.40
5	55:45	1	37.5	3.79	12284	1.42
6	55:45	0.8	37.5	4.75	14355	1.32
7	55:45	1.2	35	3.18	10650	1.46
8	55:45	1	35	3.82	12259	1.22
9	55:45	0.8	35	4.77	13989	1.34
10	50:50	1.2	40	3.56	10860	1.11
11	50:50	1	40	4.28	12423	1.40
12	50:50	0.8	40	5.34	13634	1.39
13	50:50	1.2	37.5	3.58	10850	1.34
14	50:50	1	37.5	4.30	12506	1.25
15	50:50	0.8	37.5	5.36	13543	1.26
16	50:50	1.2	35	3.60	10899	1.37
17	50:50	1	35	4.32	12300	1.25
18	50:50	0.8	35	5.46	13486	1.31
19	45:55	1.2	40	4.30	11213	1.23
20	45:55	1	40	5.13	12560	1.23
21	45:55	0.8	40	6.39	13687	1.24
22	45:55	1.2	37.5	4.31	11333	1.20
23	45:55	1	37.5	5.16	12516	1.22
24	45:55	0.8	37.5	6.43	13614	1.19
25	45:55	1.2	35	4.33	11173	1.21
26	45:55	1	35	5.20	12480	1.21
27	45:55	0.8	35	6.48	13387	1.23

experimental design allowed for the simultaneous evaluation of three independent variables (factors) at three different levels each. The optimized trial conditions, including a mobile phase ratio of 50:50 (ACN: Water), a flow rate of 1.0 mL min, and a column temperature of 37.5°C, were identified and derived from the Design Expert 11 software. The significance of the CPPs and CQAs was successfully studied by applying this factorial design, ultimately leading to the determination of a robust “design space” for method operation using the Design Expert 11 software. The optimized result was calculated by using the following Quadratic Model equation, $Y = b_0 + b_1A + b_2B + b_3C + b_{11}A^2 + b_{22}B^2 + b_{33}C^2 + b_{12}AB + b_{13}AC + b_{23}BC$

Risk Assessment

A crucial step in method development involves selecting an optimized final method that demonstrates efficiency

and sustained operability throughout the product’s entire lifecycle. To achieve this, a risk-based approach, grounded in the QbD principles outlined in ICH Q8 and ICH Q9 guidelines, was employed for method evaluation, specifically focusing on robustness and ruggedness studies. These studies meticulously assessed the method’s parameters and its performance under various conditions, including different laboratories, chemical batches, analysts, instruments, reagents, and testing days.^[18,23]

Implementing a Control Strategy

Once the method is developed, it’s essential to implement a control strategy. This strategy is built upon the analytical target profile set during development. Essentially, an analytical control strategy is a planned set of controls derived from understanding various parameters, including

its fitness for purpose, the analytical procedure itself, and effective risk management. These parameters collectively ensure that both the method's performance and its quality outputs remain within the predefined analytical target profile. A comprehensive analytical control strategy was designed to cover operations related to sample preparation, measurement, and replicate control.^[20]

Continual Improvement for Analytical Lifecycle Management

The most effective approach to managing the analytical lifecycle involves continual improvement. This can be achieved through consistent monitoring of quality consistency and periodic maintenance of HPLC instruments, computers, and related software and apparatus within the laboratory. Such practices ensure ongoing optimal performance and reliability.^[21]

Analytical Method Validation

Method validation provides documented evidence offering a high degree of assurance that a specific analytical process is suitable for its intended use. The developed HPLC method for the estimation of Rivaroxaban was validated in accordance with ICH Q2 (R2) guidelines.^[23]

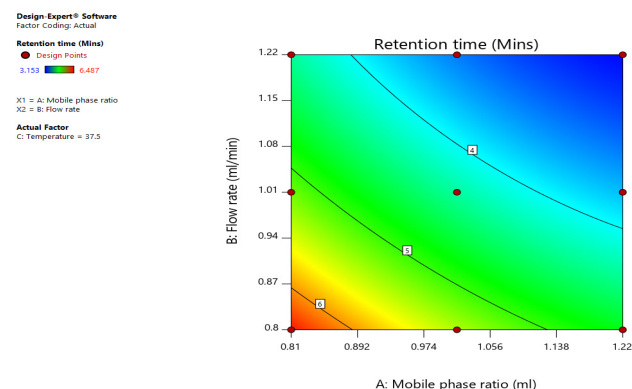


Figure 2: Surface plot for effect of combination of factors on Y_1 retention time of Rivaroxaban by using Box Behnken Design

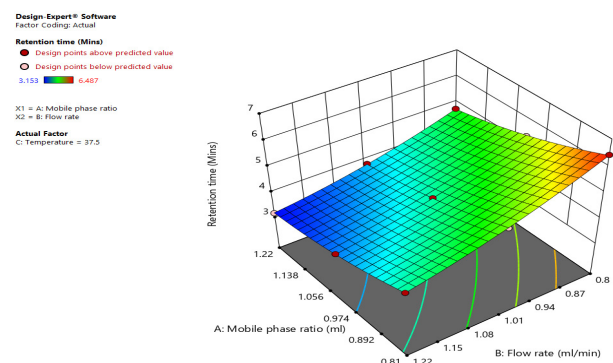


Figure 3: 3D surface plot for effect of combination of factors on Y_1 retention time of Rivaroxaban by using Box Behnken Design

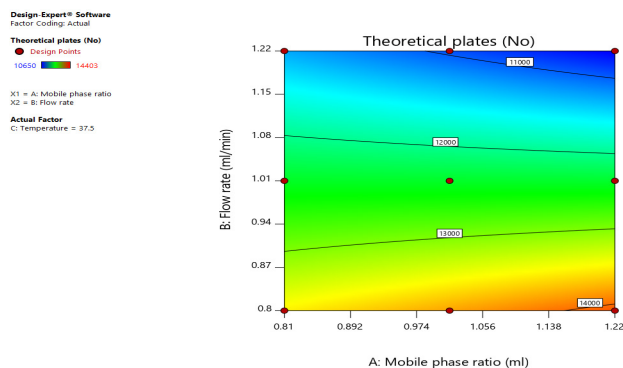


Figure 4: Surface plot for effect of combination of factors on Y_2 Theoretical Plates of Rivaroxaban by using Box Behnken Design

Results And Discussion

A total of 27 trials were conducted, and the software analyzed the response data to generate a quadratic model, $Y = b_0 + b_1A + b_2B + b_3C + b_{11}A^2 + b_{22}B^2 + b_{33}C^2 + b_{12}AB + b_{13}AC + b_{23}BC$, which described the relationship between the factors and responses. The trial with a mobile phase ratio of 50:50 (ACN: Water), flow rate of 1.0 mL/min, and column temperature of 37.5°C was identified as optimal, yielding a retention time of 4.307 minutes, theoretical plates of 12,506, and a peak area of 1,186,691. This condition was chosen because it provided a balanced combination of efficient separation, high resolution, and robust performance, as confirmed by the design space and response surface plots, ensuring the method's suitability for accurate and reliable quantification of Rivaroxaban in routine quality control.

Method Validation

The proposed method was validated as to Linearity, Range, Precision, Accuracy, Robustness, LOD, and LOQ according to the ICH guidelines (Q_2R_2).

Assay

In pharmaceuticals, an assay is a laboratory procedure used to determine the presence, amount, or activity of a specific substance, often a drug or its active ingredient, in a sample. It helps assess the quality and purity of pharmaceutical products. The %Assay was found to be 99.90% which is within the acceptable range as per guidelines.

Linearity

Linearity in an analytical method refers to its capability, within a defined range, to produce results that are directly proportional to the concentration of the analyte present in the sample. To assess linearity for RIV, a calibration curve was generated by plotting known concentrations against their corresponding peak area ratios. The results demonstrated a linear relationship up to a concentration of 30 µg/mL. A total of six standard solutions within this linear range—

Table 4: Optimized Trial

Final trial	Mobile phase ratio (v/v) (X_1)	Flow Rate (X_2)	Temperature (X_3)	Retention time (Y_1)	Theoretical Plates (Y_2)	Assymetry (Y_3)
14	50:50	1.0 mL /min	37.5 °C	4.307	12506	1.25

including concentrations of 5.0, 10.0, 15.0, 20.0, 25.0, and 30.0 µg/mL—were prepared and analyzed using the HPLC system. The linearity of the method was confirmed through linear regression analysis, from which the calibration curve equations were derived. The R^2 value was found to be 0.9993 which is within the acceptable limits.

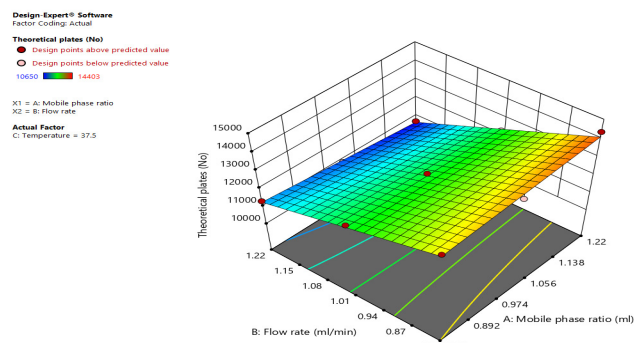


Figure 5: 3D surface plot for effect of combination of factors on Y_2 Theoretical Plates of Rivaroxaban by using Box Behnken Design

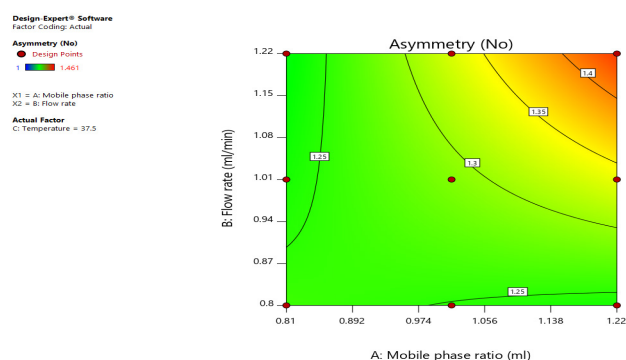


Figure 6: Surface plot for effect of combination of factors on Y_3 Assymetry of Rivaroxaban by using Box Behnken Design

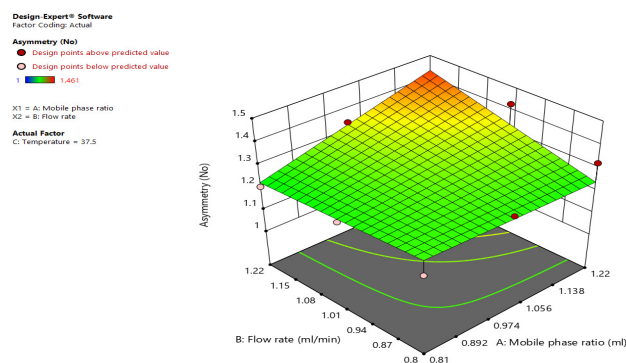


Figure 7: 3D Surface plot for effect of combination of factors on Y_3 Assymetry of Rivaroxaban by using Box Behnken Design

Sensitivity

The sensitivity of the developed method was assessed by determining the Limit of Detection (LOD) and Limit of Quantification (LOQ). These parameters were calculated based on the standard deviation of the response and the slope of the calibration curve, using the formulas $LOD = 3.3 \times (\sigma/S)$ and $LOQ = 10 \times (\sigma/S)$, where σ represents the standard deviation of the y-intercepts and S is the slope of the calibration line. The calculated LOD and LOQ values indicate that the method is capable of reliably detecting and quantifying low concentrations of RIV, confirming its suitability for routine analysis.

LOD: 0.026 µg/mL

LOQ: 0.079 µg/mL

Precision

The precision of the analytical method was evaluated by assessing both intra-day (repeatability) and inter-day (intermediate precision) variations. Multiple injections of standard solutions at the same concentration levels were analyzed within the same day and across three consecutive days. The precision was expressed as the relative standard deviation (RSD%) of the measured peak areas. The low RSD values obtained in both intra-day and inter-day studies demonstrated the method's high level of reproducibility and reliability for consistent quantitative analysis. The precision results were found to be <0.5% which is within the acceptable limits.

Accuracy

The accuracy of the developed method was determined by recovery studies, which involved the analysis of known amounts of RIV added to pre-analyzed samples. The test was conducted at three different concentration levels within the linear range. Each level was analyzed in triplicate, and the percentage recovery was calculated by comparing the measured concentrations to the known added amounts. The recovery results, which were within acceptable limits, confirmed that the method is accurate and free from interference by sample matrix components. The % recovery results was found to be between 98-102% which is within the acceptable limits.

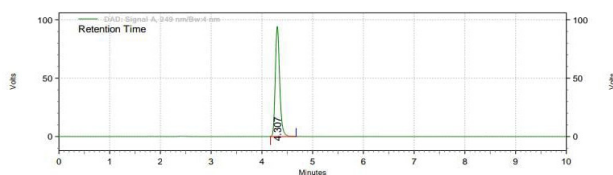
Robustness

The robustness of the analytical method was assessed by making deliberate, small variations in method parameters, such as changes in detection wavelength. These modified conditions were applied to the analysis of RIV standard solutions to evaluate the impact on retention time and peak area. The results showed minimal variation, with acceptable

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Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\TRIAL14_19032025.dat
Method: E:\EZChrom Elite\Enterprise\Projects\Default\Method\RIVA_SYSTEM SUITABILITY.met
Acquired: 3/20/2025 12:57:35 PM
Printed: 4/15/2025 2:28:24 PM



DAD: Signal A, 249 nm/Bw:4 nm/Results

Retention Time	Area	Area %	Height	Height %	Asymmetry	Theoretical plates (USP)	Asymmetry (10%)
4.307	1186691	100.00	197677	100.00	1.27610	12506	1.25008
Totals	1186691	100.00	197677	100.00			

Figure 8: HPLC Graph of Optimized Trial

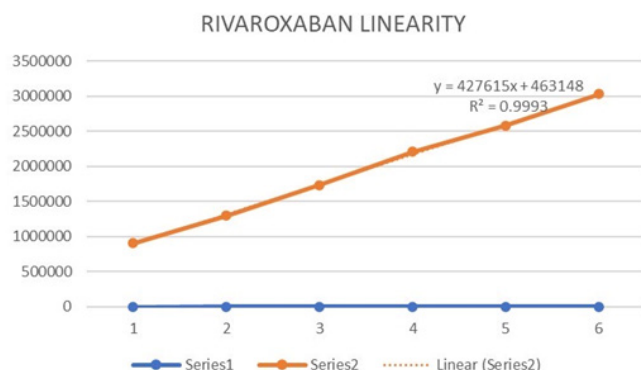


Figure 9: Linearity graph of Rivaroxaban

relative standard deviation (RSD%) values, indicating that the method remains reliable and consistent under slight changes in experimental conditions.

The %RSD was found to be 0.32% which is within the acceptable limits.

Table 5: Recovery Data of the Method

Sample	Solution A formulation	Solution B standard	Area	%Recovery
80%	1.0	0.8	1431798	100.01
80%	1.0	0.8	1427294	99.70
80%	1.0	0.8	1435785	100.29
100%	1.0	1.0	1572930	99.71
100%	1.0	1.0	1576166	99.91
100%	1.0	1.0	1583434	100.38
120%	1.0	1.2	1752249	99.88
120%	1.0	1.2	1758115	100.21
120%	1.0	1.2	1752878	99.21

Discussion

A systematic optimization approach was undertaken, involving 27 trials conducted using a 3³ factorial design, with the aid of Design Expert 11 software. This process aimed to refine key Critical Process Parameters (CPPs), namely flow rate, mobile phase composition, and detection wavelength. Analysis of the response data generated a quadratic model describing the relationships between these factors and the method's Critical Quality Attributes (CQAs). The optimal conditions identified, specifically from trial 14, included a mobile phase ratio of 50:50 (acetonitrile: water), a flow rate of 1.0 mL/min, and a column temperature of 37.5°C. These parameters yielded a retention time of 4.307 minutes, 12,506 theoretical plates, and a peak area of 1,186,691. This specific combination was chosen due to its demonstrated balance of efficient separation, high resolution, and robust performance, which was further supported by the design space and response surface plots, ensuring the method's suitability for accurate and reliable routine quality control of Rivaroxaban.

Subsequent to development, the HPLC method underwent rigorous validation in accordance with ICH Q2 (R2) guidelines. This comprehensive validation confirmed the method's performance across essential analytical attributes, including linearity, range, precision (both intra-day and inter-day), accuracy, robustness, Limit of Detection (LOD), and Limit of Quantification (LOQ). The method exhibited excellent linearity over a range of 5–30 ppm, evidenced by an R² value of 0.9993. Precision studies consistently yielded low Relative Standard Deviation (RSD) values (below 0.5%), highlighting the method's high reproducibility. Accuracy, determined through recovery studies at various concentration levels, showed results between 98–102%, confirming its reliability and freedom from matrix interference. Furthermore, the robustness assessment, which involved minor deliberate variations in parameters like detection wavelength, showed minimal impact on results (0.32% RSD), ensuring consistent performance under slight changes in experimental conditions. The calculated LOD and LOQ values were 0.026 µg/mL and 0.079 µg/mL, respectively, affirming the method's sensitivity for detecting and quantifying low concentrations of Rivaroxaban.

Conclusion

By using a robust Quality by Design (QbD) approach, we have successfully developed and validated an RP-HPLC method for the quantitative analysis of Rivaroxaban (RIV) in bulk and tablet dosage forms. As per the literature survey, this is the first method for RIV analysis to leverage a dedicated QbD strategy, leading to a thoroughly understood and highly dependable analytical procedure. The systematic development ensured rigorous validation in accordance with ICH guidelines, confirming its performance in terms of selectivity, accuracy, linearity, precision (intra- and inter-day), sensitivity, robustness, and ruggedness. A key practical benefit of this QbD-informed development is the

method's streamlined mobile phase, which requires no buffer preparations or ion-pairing reagents, along with its quick run time, and statistically proven. These features collectively enhance the method's efficiency and make it ideal for high-throughput routine quality control of numerous samples.

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